REMARKS

Reconsideration of this application is respectfully requested. An editorial amendment has been made to claim 5. Claims 1, 6, 7, 36, and 44 have been amended as discussed below. Claims 58-60 have been added. Support for claims 58-60 is found at, for example, paragraphs 14, 33, 43, 44, 51, 125, 126, and 131 of the published version of this application (US 2010/0008984). Claims 1, 3–10, 16-20, 22-29, 31–34, 36–44 and 51–60 are pending and at issue.

Claims 38 and 39 have been objected to for including the incorrect status identifier. The listing of claims submitted with this amendment correctly identifies these claims as "previously presented."

Indefiniteness Rejection

Claims 6, 7, 36, 37, and 44 have been rejected as indefinite. Claims 6, 7, and 44 have been rejected for lack of antecedent basis due to the terms "the vehicle" (in claims 6 and 7) and "the active ingredient" (in claim 44). Claims 6 and 7 have been amended to replace the term "vehicle" with "polyethylene glycol and poloxamer." Claim 44 has been amended to replace the term "active ingredient" with "tacrolimus."

The Examiner also contends that the phrases "substituted and/or unsubstituted diglycerides" and "substituted and/or unsubstituted triglycerides" in claim 36 are indefinite since the specific substituents are not defined. While Applicants respectfully disagree, in order to expedite prosecution, these phrases have been removed from claim 36.

In view of the foregoing, Applicants respectfully request withdrawal of this rejection.

Obviousness Rejection Over Koretke in view of Kelm, Drugs.Com, Yang, and Kjaergaard

Claims 1, 3-10, 16-20, 22-26, 31-34, 36-44, and 56 have been rejected as obvious over Koretke (WO 01/95939) in view of Kelm (WO 93/23022) and Drugs.com ("Tacrolimus (Systemic)", Drugs.com, August 1997), as evidenced by Yang (*Int J Pharmaceutics*, 1992, 86(2-3), p.247-257, abstract only) and Kjaergaard ("Prilling – Multiple Core Encapsulation", GEA Process Engineering, 8/2000, p.1-10).

A. The Invention and its Surprising Benefits

The presently claimed invention is a solid pharmaceutical composition comprising tacrolimus containing particles. The particles comprise (i) tacrolimus in polyethylene glycol (PEG) and poloxamer, and (ii) a solid carrier. Furthermore, the tacrolimus is present in the solid pharmaceutical composition at a concentration of 0.01 to 15 w/w%. The present inventors have surprisingly discovered that the presently claimed formulation provides enhanced bioavailability as well as lower fluctuation and swing *in vivo* than other tacrolimus formulations, including Prograf and Advagraf which are marketed by Astellas Pharma.[1]

Tacrolimus is an immunosuppressant used to prevent organ rejection in patients who have received liver, kidney, or heart transplants. Tacrolimus, however, has a narrow therapeutic window. "Subtherapeutic tacrolimus blood concentrations increase the risk of transplant rejection enormously, while high tacrolimus blood concentrations may lead to severe side effects such as nephrotoxicity, neurotoxicity and hyperglycemia." Op den Buijsch, et al., *Fundamental & Clinical Pharmacology*, 21:427-435 (2007) (Exhibit A). It is, therefore, desirable to have a tacrolimus dosage form which provides consistent blood levels of tacrolimus in these patients. The presently claimed pharmaceutical composition achieves this goal.

Two measurements for the consistency of a drug level include "fluctuation" and "swing." The results of a human clinical study comparing the presently claimed formulation to Prograf is

[1] Astellas Pharma markets Prograf in the U.S. and Europe, and Advagraf in Europe.

provided in Example 19 of US 2010/0105717 (Exhibit B, p. 27-33). (Both the present application and US 2010/0105717 are assigned to LifeCycle Pharma A/S.) The clinical study involved 47 kidney transplant patients who prior to the study were being treated with Prograf (a twice daily formulation of tacrolimus). The patients were kept on Prograf for the first 7 days of the trial and then converted to a formulation of the present invention (referred to as "LCP Tacro")[2] at a ratio of 1 mg Prograf to 0.66-0.80 mg LCP-Tacro, without a further change in the dose of tacrolimus. The reduced amount of tacrolimus was used since it was previously determined that LCP-Tacro provides significantly greater systemic exposure to the tacrolimus. The bioavailability (AUC_t) of LCP Tacro was 37-39% greater than that of Prograf (using dose corrected data). *See* the table at the bottom of page 28 of US 2010/0105717. LCP Tacro also exhibited a significantly lower degree of fluctuation and swing compared to Prograf. The degree of fluctuation and swing were reduced by approximately 40% and 37%, respectively. These results are shown in the table below.

Parameter	Prograf	LCP Tacro	
	Day 7	Day 14	Day 21
AUC_t (ng·hr/mL)[3]	34.81	47.73	48.3
% increase relative to Prograf		37.12%	38.75%
Fluctuation (%)	127.41	73.24	77.04
% decrease relative to Prograf		42.52%	39.53%
Swing (%)	174.55	102.80	110.07
% decrease relative to Prograf		41.11%	36.94%

The presently claimed formulation also provides a superior pharmacokinetic profile compared to Advagraf, a once daily formulation also marketed by Astellas Pharma. The results of a human clinical study comparing the presently claimed formulation to Advagraf is provided in Example 20 of US 2010/0105717 (Exhibit B, p. 33-36). Subjects were administered either

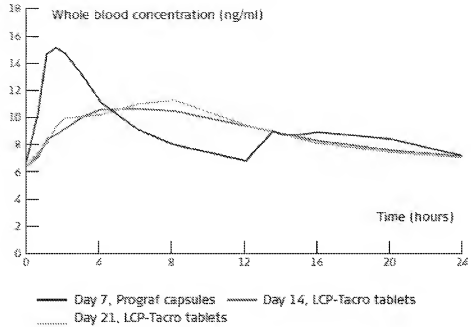
[2] The formulation of LCP-Tacro is shown in the last table in the right column on page 36 of US 2010/0105717.
[3] The AUC_t values reported here for Prograf and LCP-Tacro are dose corrected values. As mentioned above, patients received 0.66-0.80 mg LCP-Tacro for each 1 mg of Prograf.

one 2 mg tablet of the present invention (also referred to as "LCP Tacro") or two 1 mg capsules of Advagraf. The pharmacokinetic parameters of tacrolimus in the subjects was measured on day 10 and is reported in Tables 20-3 (LCP Tacro) and 20-4 (Advagraf) of US 2010/0105717 (p. 35). The fluctuation and swing measurements for LCP Tacro were nearly half that of Advagraf (shown below):

Parameter	LCP Tacro (Table 20-3)	Advagraf (Table 20-4)
Fluctuation (%)	60.92	106.46
Swing (%)	78.16	150.98

Additionally, the bioavailability of tacrolimus from LCP Tacro (AUC_{tau} = 133.99 ng·hr/mL) was about 50% greater than Advagraf (AUC_{tau} = 89.86 ng·hr/mL). *See also* Abstract #284 of the 2008 American Transplant Congress (ATC) (showing that the bioavailability of the presently claimed formulation has approximately 50% greater bioavailability than Advagraf after 10 days of treatment) (Exhibit C).

As shown by the clinical data above, the presently claimed formulation provides greater systemic exposure to tacrolimus with a lower degree of fluctuation and swing. Incredibly, the presently claimed formulation provides a nearly constant level of tacrolimus over 24 hours as shown by Figure 5 of US 2010/0105717 (reproduced below with modified ledger).

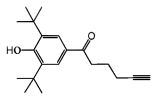


The "flat" pharmacokinetics provided by the presently claimed formulation avoids the peaks and valleys associated with Prograf and Advagraf, and therefore offers consistent pharmacokinetic profile and efficacy, and reliability of performance. Further, a lower effective dosage can be used compared to Prograf and Advagraf, thus possibly reducing the severity of or avoiding the side effects observed with Prograf and Advagraf. The superior results achieved with the presently claimed formulation are not disclosed or suggested by Koretke, Kelm, or Drugs.com.

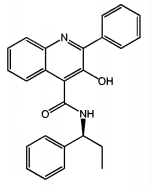
Tacrolimus is a poorly soluble drug and, as a result, is difficult to make highly bioavailable. Astellas which has been working with tacrolimus for at least two decades developed Prograf and Advagraf and would therefore have had the motivation to have developed and brought to market a formulation with greater bioavailability. Astellas' currently marketed products, Prograf and Advagraf, however, have significantly lower bioavailability and therefore require doses at least 25% greater than the presently claimed formulation to achieve similar bioavailability.

B. No Motivation to Form Tacrolimus Particles Containing PEG and Poloxamer

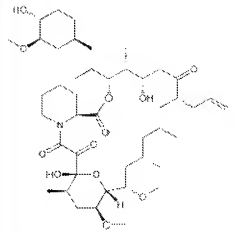
Koretke does not mention the drug tacrolimus. The only drugs specifically referred to by Koretke are neurokinin-3 receptor antagonists for treating chronic obstructive pulmonary disorder and urinary incontinence, and the compound (S)-(-)-N-(α-ethylbenzyl)-3-hydroxy-2-phenylquinoline-4-carboxamide ("the Quinoline Compound") (Koretke, p. 4, lines 10-21). Tacrolimus is typically used to prevent organ rejection, not chronic obstructive pulmonary disorder or urinary incontinence. Tacrolimus also has a significantly different chemical structure from the Quinoline Compound as shown below.



Tebufelone (Kelm)



The Quinoline Compound (Koretke)



Tacrolimus

Kelm also does not disclose or suggest a formulation containing tacrolimus. Rather, Kelm is solely directed to formulations containing the drug tebufelone. As can be seen above, tacrolimus is structurally very different from tebufelone and the Quinoline Compound. For instance, tacrolimus is a non-aromatic macrolide having a molecular weight of over 800 g/mol, whereas tebufelone and the Quinoline Compound are much smaller (~300 g/mol and ~382 g/mol, respectively) and have aromatic groups. Due to these structural differences, one skilled in the art would not have assumed that a delivery system suitable for tebufelone or the Quinoline Compound would be effective for tacrolimus.

Koretke broadly discloses that his formulation is useful for "any poorly soluble, poorly wettable compound that melts without decomposition below the flash point of polyethylene glycol." *See* Koretke at page 4, lines 22-24. A skilled artisan, however, would not assume that Koretke's delivery system would work for all poorly soluble drugs, since there is no single known method for solubilizing all poorly soluble drugs. Numerous techniques and hundreds (if not thousands) of delivery systems have been developed for solubilizing such drugs. The effectiveness of these techniques and delivery systems varies significantly from drug to drug, and a formulator cannot *a priori* predict which techniques and delivery systems will be successful for a given drug. Accordingly, a formulation scientist would not have reasonably expected the enhanced delivery of tacrolimus achieved with the presently claimed solid pharmaceutical composition based on Koretke's formulation of the Quinoline Compound or Kelm's formulation of tebufelone.

While Drugs.com discloses tacrolimus, it does not disclose or suggest preparing tacrolimus particles containing PEG and poloxamer. Accordingly, a skilled artisan would not have had the motivation to specifically choose to formulate tacrolimus using the delivery system described in Koretke based on Drugs.com.

Koretke also does not disclose or suggest *particles* containing a drug, PEG and poloxamer. In the sole example in Koretke, the Quinoline Compound is co-melted with PEG and poloxamer and poured into a capsule (see, for example, p. 7, lines 8-26, of Koretke). Koretke does not disclose or suggest that particles are formed.

The Examiner argues that Kelm provided the motivation to form particles from Koretke's formulation. However, particles are not formed in the sole example of Kelm which used PEG and poloxamer. In Example 4 (p. 7-8 of Kelm), Kelm melts and blends the components in his formulation to form a homogenous liquid which is then filled into molds and allowed to solidify. Kelm, therefore, suggests that a solidified melt is preferred over particulates.

The Examiner further argues that Kelm suggests prilling the melt composition in Koretke to form particles (p. 7, last paragraph, of the January 13, 2011 Office Action). The Examiner concludes that "[o]ne of ordinary skill in the art ... would have recognized that by forming particles of the melt composition of Koretke et al. would increase the surface area of the composition, thereby improving the aqueous solubility of the composition in the gut after oral administration" (p. 8, second paragraph, of the Office Action). Koretke, however, expressly teaches away from altering his solid dispersion by physical means, such as milling which increases the surface area of the formulation:

> Preferred solid dispersions of this invention may be filled into capsules or molds prior to solidification. Alteration of the solid dispersion by physical means (i. e., additional energy added) from the original cooled solid form yielded drastically different solubilization due to uncontrolled erosion rate and nucleation of the drug substance in the milled high surface area formulation. This property distinguishes this invention from known solid dispersion dosage forms in which solid dispersion of drug and PEG were milled and filled into capsules or tableted.

(Koretke, p. 6, lines 31-38, emphasis added). Thus, according to Koretke, alteration of the solid dispersion by physical means can yield "drastically different solubilization" of the drug. *See also* p. 2, lines 27-36, and p. 4, lines 1-9, of Koretke (teaching that Koretke's formulation contains the drug in *amorphous* form, and the criticality of ensuring that the drug does not crystallize (nucleate)). A skilled artisan reading Koretke would, therefore, not have been motivated to prill the Koretke formulation.

For the foregoing reasons, one of ordinary skill would not have had any motivation to form particles of tacrolimus, PEG, and poloxamer, or a reasonable expectation that such a combination could successfully be used to prepare a highly bioavailable tacrolimus composition.

C. Tacrolimus is Unsuitable for the Delivery System in Koretke and Kelm

The applicants have further found that tacrolimus is unsuitable for use in Koretke's and Kelm's delivery system. As discussed in greater detail below, Koretke and Kelm require that the drug be melted without decomposition. Tacrolimus, however, readily degrades when heated to its melting point yielding a product unsuitable as a pharmaceutical.

Koretke repeatedly states that his delivery system is only suitable for drugs that melt without decomposition below the flashpoint of polyethylene glycol.

> [T]his invention is useful for **any poorly water soluble, poorly wetable compound that melts without decomposition** below the flash point of polyethylene glycol.

(Koretke, p. 4, lines 22-24, emphasis added).

> The instant compositions consist essentially of … **a drug which melts without decomposition** at a temperature below the flashpoint of the PEG.

(Koretke, p. 4, lines 26-28, emphasis added)

> **The drug should melt without decomposition** at a temperature below the flashpoint of the PEG.

(Koretke, p. 5, lines 5-6, emphasis added)

> [T]his invention relates to a solid dispersion pharmaceutical composition consisting essentially of a co-melt of a poloxamer surfactant, a mid-molecular weight polyethylene glycol and **a therapeutically active compound that melts without decomposition** at a temperature below the flash point of polyethylene glycol.

(Koretke, p. 1, lines 7-11, emphasis added)

Importantly, this requirement inherently requires the drug to melt without decomposition. (In any event, the melting point of tacrolimus is ~126-130° C, which is significantly below the flashpoint of PEG 6000, which is about 246° C (Koretke, p. 6, lines 3).)

Koretke also requires heating the drug to at least its melting point in the preparation of his solid dispersion. For instance, Koretke defines a "solid dispersion" as a material which is solid at room temperature, which was produced by "blending ***melted*** drug with" other components (Koretke, p. 4, lines 32-36, emphasis added). *See also* Koretke, p. 6, lines 25-27, emphasis added ("The fast release solid dispersions … are preferably made by ***melting the drug***, the polyethylene glycol and the poloxamer surfactant together with mixing, to form a homogenous melt mixture"). The melting of the drug is necessary to convert it into an amorphous state, which is maintained by the PEG and poloxamer (Koretke, page 4, lines 1-3).

As discussed in the Declaration of Nikolaj Skak submitted herewith, the preparation process described in Koretke was repeated using Koretke's preferred components of PEG 6000 and poloxamer 188 at Koretke's preferred PEG-poloxamer-drug weight ratio of 15:1:4 (Koretke, p. 5, lines 33-37, p. 6, lines 4-6, and p. 7, lines 3-5; Skak Declaration, ¶4 and 6). The mixture of PEG, poloxamer, and tacrolimus was heated to the lowest end of the melting point range of tacrolimus (126° C), and the amount of tacrolimus and three degradation products were measured (Skak Declaration, ¶4-8). The experiment was repeated three times, and each product was analyzed twice (*id.*, ¶9). The results are shown in Table 2 on page 4 of the Skak Declaration.

About 14% of the initial amount of tacrolimus was lost during each run. Furthermore, about 2.2 to 2.5% of the tacrolimus degraded to its C8-epimer. According to ICH guidelines, pharmaceutical products are not permitted to have more than 0.5% of any single degradation product, unless additional studies have been performed and establish the safety of the degradation product at the elevated levels observed (Skak Declaration, ¶10). According to Mr. Skak, a pharmaceutical scientist with considerable experience,

> To my knowledge, neither the U.S. Food and Drug Administration nor the European Medicines Agency has found a tacrolimus product containing 2.4% or more of the C8-epimer to be safe based on such studies. Accordingly, such a product is not considered pharmaceutically acceptable. Because of the high level of degradation product and double digit reduction in tacrolimus, a skilled artisan would not consider the Koretke process viable for making pharmaceutical formulations of tacrolimus.

(*id.*)

Similarly, Kelm states that his solid dispersion is "preferably made by ***melting*** the tebufelone and the poloxamer surfactant together, with mixing, to form a homogenous melt mixture" (Kelm, p. 6, lines 18-20, emphasis added). No other method for making the solid dispersion is taught by Kelm. Furthermore, in each of the examples in Kelm, the tebufelone is heated at a temperature 5 or 15° C above its melting point. Tebufelone has a melting point of 70° C (Kelm, p. 2, line 34), and is heated to 75 or 85° C in the examples until a homogenous liquid is formed. *See* Examples 1-4 on p. 7-8 of Kelm.

Because tacrolimus undergoes significant degradation upon melting, a skilled artisan would not consider it suitable for use in the processes taught by Koretke and Kelm.

The other cited references (Drugs.com, Yang, and Kjaergaard) do not cure the deficiencies of Koretke and Kelm. Drugs.com, Yang, and Kjaergaard do not disclose or suggest tacrolimus particles containing PEG and poloxamer, as recited in the pending claims.

For the reasons stated above, Koretke, Kelm, Drugs.com, Yang and Kjaergaard, taken alone or together do not render obvious the present claims. Applicants respectfully request, therefore, that the rejection be withdrawn.

Obviousness Rejection Over Patel in view of Lee

Claims 1, 3-10, 16-20, 22-29, 31-34, 36-44, and 51-57 have been rejected as obvious over Patel (US 2003/0180352) in view of Lee (US 6,168,806).

The Examiner contends that Patel "disclose sold pharmaceutical compositions comprising tacrolimus on a solid carrier, and compositions comprising other water insoluble agents with poloxamers (e.g., poloxamer 188) or polyethylene glycols on solid carriers" (Page 11

of the Office Action). The disclosure in Patel is so general, however, that it teaches nothing more than combining ***any*** drug with ***any*** surfactant. No guidance is given as to how to select and formulate specific active ingredients such as fenofibrate. Additionally, neither Patel nor Lee disclose or suggest the surprisingly enhanced bioavailability achieved by the presently claimed fenofibrate tablet.

The Summary of the Invention section of Patel describes five embodiments of a solid pharmaceutical composition (¶ 31-35). The solid pharmaceutical composition in each embodiment contains a surfactant in a solid carrier. Other than stating that the surfactant is hydrophilic or lipophilic, and that the surfactant may be incorporated in an encapsulation coat in the solid carrier, no other specifics are provided. The descriptions of the first, second, and fourth embodiments are so broad that they do not even recite the presence of an active ingredient (¶ 31, 32, and 34).

The Detailed Description section of Patel provides list after list of possible active ingredients, surfactants and other excipients. At paragraph 104 (p. 8), Patel states that the active ingredient can be of any type: "The active agent of the present invention can be hydrophobic, amphipilic, or hydrophilic." Hydrophobic active agents are said to have an aqueous solubility of less than 1% (by weight), while hydrophilic and amphiphilic active agents have an aqueous solubility of at least 0.1% (*id.*). Patel thus teaches that *any* active ingredient can be used. The list of possible active ingredients **spans 8 pages** of Patel and includes hundreds of active ingredients from practically every known therapeutic class (paragraphs 56-103 and 106-115, p. 4-11).

Patel also teaches that *any* surfactant can be used:

> Various embodiments of the invention, as described in more detail below, include a hydrophilic surfactant. …
>
> Likewise, various embodiments of the invention include a lipophilic additive, which can be a lipophilic surfactant …

(paragraphs 144 and 145). Hydrophilic surfactants are said to have a hydrophilic-lipophilic balance (HLB) of greater than about 10, while lipophilic surfactants have an HLB value of less than about 10 (paragraphs 146 and 147). Patel thus teaches that *any* surfactant can be used. The specification further provides 20 general categories of surfactants (sections 2.1 to 2.20) and lists hundreds if not thousands of possible surfactants **spanning 13 pages** of the specification (pages 13-25). The specification provides nothing more than a handbook of surfactants.

Patel further states that *any* process can be used to prepare the formulations:

> The compositions of the present invention can be processed by agglomeration, air suspension chilling, air suspension drying, balling, coacervation, coating, comminution, compression, cryopelletization, encapsulation, extrusion, wet granulation, dry granulation, homogenization, inclusion complexation, lyophilization, melting, microencapsulation, mixing, molding, pan coating, solvent dehydration, sonication, spheronization, spray chilling, spray congealing, spray drying, or other processes known in the art.
>
> The compositions of the present invention can be prepared by a variety of processes to apply an encapsulation coat onto a substrate or to form a substrate-free solid carrier …

(paragraphs 272 and 310, p. 29 and 32).

The number of possible combinations of active ingredients and surfactants in Patel is nearly infinite. An invention "composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). More recently, the Court of Appeals for the Federal Circuit stated:

> [I]t is not enough to simply show that the references disclose the claim limitations; in addition, 'it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does.'

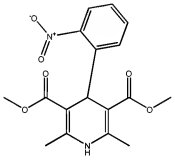
Transocean Offshore Deepwater Drilling, Inc. v. Maersk Contractors USA, Inc., 617 F.3d 1296, 2010 WL 3257312 at *4 (Fed. Cir. 2010) (*quoting KSR*, 550 U.S. at 401). Ultimately, "[i]n

determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995) (internal quotations omitted). Clearly, as shown above, Patel would not have prompted a skilled artisan to specifically formulate fenofibrate in a hydrophilic vehicle of poloxamer and a hydrophilic polymer. It is improper to use hindsight to pick and choose isolated elements from the prior art and combine them to yield the invention without some suggestion to do so. *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008) ("the district court is not to rely on hindsight"); *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966) (the obviousness inquiry must "guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention in issue").

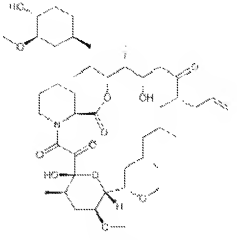
Patel provides a single example of a tacrolimus formulation. *See* Example 20 at paragraph 425, p. 41. This example appears to be prophetic since Patel states that "Examples 13-28 illustrate compositions that **can be** prepared according to the present invention" (paragraph 417, p. 41). Furthermore, Patel does not describe how Example 20 is prepared, but merely states that the formulation in Example 20 "can be prepared in the absence of the active ingredients and appropriate amounts of the active ingredients in any given dosage form then can be administered together or separately with the composition" (*id.*). Example 20 is thus simply a list of the components and their respective amounts. Notably, the formulation does not include PEG or poloxamer, but includes two *lipophilic* surfactants, distilled monoglycerides and deoxycholic acid. *See* paragraph 399 (characterizing both as lipophilic). This example therefore does not suggest a formulation in which tacrolimus is in a *hydrophilic* vehicle of PEG and a poloxamer as recited in the pending claims.

In summary, Patel teaches nothing more than preparing a solid pharmaceutical composition containing a drug and a surfactant. Patel provides absolutely no guidance as to the selection of surfactants, or as to how to formulate a tacrolimus tablet which does not exhibit a food effect.

Lee also does not disclose or suggest particles containing (i) tacrolimus in PEG and poloxamer and (ii) a solid carrier. Rather, Lee is solely directed to a nifedipine formulation. As shown below, tacrolimus is structurally very different from nifedipine.



Nifedipine



Tacrolimus

Tacrolimus is a non-aromatic macrolide having a molecular weight of over 800 g/mol, whereas nifedipine is a much smaller molecule having a couple of aromatic rings and a molecular weight of ~346 g/mol. Due to these structural differences, one skilled in the art would not have assumed that a delivery system suitable for nifedipine would be effective for tacrolimus.

Additionally, the presently claimed tacrolimus formulation provides enhanced bioavailability and lower fluctuation and swing as compared to other tacrolimus formulations (Prograf and Advagraf), as discussed above with respect to the rejection over Koretke, Kelm, and Drugs.com. Neither Patel nor Lee disclose or suggest that tacrolimus particles containing PEG and poloxamer would exhibit such enhanced bioavailability or reduced fluctuation and swing.

For the foregoing reasons, Patel alone or in combination with Lee fails to render obvious the presently claimed formulation.

In view of the above amendments and remarks, Applicant believes the pending application is in condition for allowance.

Dated: February 14, 2011

Respectfully submitted,

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